Alzheimer's Disease

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I want to thank the Senate Special Committee on Aging and the Alliance for Aging Research for sponsoring today's forum. It is a pleasure to be here today and to share with you news about the exciting pace of scientific discoveries and strategies we are pursuing at the National Institute on Aging regarding Alzheimer's disease (AD). As the Alliance's report makes clear, the need to prevent or delay the onset of Alzheimer's disease is paramount - particularly as we enter the next century and confront the threat of an Alzheimer's disease epidemic.

According to the Alzheimer's Association, an estimated four million Americans now suffer with Alzheimer's disease and by the time the "baby boom" generation reaches the age of greatest risk, as many as 14 million persons will be afflicted. Projected demographic changes force us to focus on the problem of AD as the risk of developing this disease doubles every five years after the age of 65. Some estimates place as high as 50% the proportion of persons over the age of 85 who have AD - and persons over 85 comprise our very fastest growing age group. As the population changes, not only will there be more persons with AD, but the make-up of this population will be much more diverse, requiring us to consider the special risks and needs of minority groups.

AD is a disease that slowly, steadily, and inevitably robs the patient of all sense of self and of a meaningful relationship with the outer world. The disease progresses through forgetfulness to loss of the ability to function in the home without constant supervision. It often requires a move to a nursing home and eventually results in a bedridden state of total incapacity. Throughout this the process, relatives undergo not only loss but a series of losses as the loved one slips slowly down the AD slope. The financial cost for caring for persons with dementia is estimated at $100 billion per year. This estimate does not include the toll AD exacts on relatives caring for AD patients and dealing with events that deplete them physically and emotionally, as well as financially, over the course of 10-20 years.

Until recently, memory loss and development of dementia were seen as inevitable consequences of aging, and the related loss of independence the price we had to pay for living into our 70s and beyond. However, with the recent explosion in scientific knowledge, we are beginning to understand the process of aging, the mysterious working of the brain, and how and why the mind falters in aging and completely falls apart after AD strikes. With each advance in knowledge comes insights into ways we might delay "frailty of the mind" and loss of independent function.

The AD Prevention Initiative

To capitalize on recent scientific advances and current opportunities, the NIH has launched an Alzheimer's Disease Prevention Initiative. The AD Prevention Initiative joins the resources of the National Institute on Aging (NIA) with those of other Institutes in the National Institutes of Health (NIH), other government agencies, and voluntary organizations and companies in the private sector. It aims to slow the progression of and eventually to prevent AD by:

- Using basic research to identify promising targets for preventing disease.
- Identifying new drugs and interventions.
- Starting clinical trials to stop, delay or prevent disease.

- Reducing suffering from AD to alleviating the symptoms, improving management of AD and helping caregivers cope with the disease.

The Prevention Initiative will involve coordination with other Federal agencies, drug companies, and private foundations. Within NIH, several Institutes (NIA, NINDS, NIMH, NINR), which comprise the NIH AD Working Group, are collaborating on the Prevention Initiative. Within the Federal government, ties with HCFA, the CDC, and the VA will be strengthened, as well as those to state and local agencies. The Alzheimer's Association partners with NIH staff and researchers at both local and national levels to sponsor research, workshops, and education and outreach programs. Partnerships with other not-for-profit agencies are also being developed. Finally, the NIH will continue to interact with pharmaceutical companies in basic research, drug development and testing, and, in particular, will continue to encourage small companies to apply for drug development grants. The NIH will also continue to identify partners for collaboration and encourage its grantees to build collaborative research relationships.

Launching this initiative will help ensure that the pipeline of AD research contains an increasing flow of discoveries from basic and clinical research to clinical trials and subsequent implementation of effective prevention and treatment strategies. The goal is to maintain independent life for more people and for much longer than is presently possible.

Treatments already developed to slow rate of decline or disability in AD patients

Once AD was defined clinically, scientists could discover ways in which the brain of a person with AD differed from that of a person with normal cognition. In the 1970s, scientists found that certain brain cells were dying in the brain of a person with AD, depleting levels of a brain chemical essential for memory (acetylcholine). The practical result of these discoveries was development of drugs aimed at temporarily boosting levels of acetylcholine, even though the brain cells continued to die. The two FDA-approved drugs for AD, Cognex (tacrine) and Aricept (donepezil), belong to this class of drugs and more are in development. Aricept has few side effects and recent clinical studies show that for some patients it can effectively slow the slide down the AD slope for up to 2 yers. Antioxidants, vitamin E and selegiline (which combat the free radicals generated at high levels in AD brain), have also been shown to delay important milestones in decline (e.g., loss of ability to care for oneself, moving into a nursing home) by up to 6 months. Thus, for persons with AD we can now buy some time for some people.

First steps in prediction lead to the first prevention trials

Most research, until recently, has been aimed at identifying the changes that occur in brains of AD patients who are in later stages of the disease and easily diagnosed. These changes include plaques, tangles, oxidative stress, inflammation, and loss or dysfunction of brain cells and their connections. Many of these advances were made possible by the funding of the network of Alzheimer's Disease Centers across the country, now augmented by establishment of a common Database Center in 1999. In the last couple of years, researchers have made progress in identifying persons who are at high risk for developing AD, prior to clinical diagnosis. Persons diagnosed with mild cognitive impairment (MCI) have quite severe problems with short-term memory, but are otherwise fully functional. However, they are at least 10 times more likely to develop AD in the next few years than persons who test normally for their age. Clinical and neuropsychological tests are being developed to identify these people. Brain scans of different kinds are showing that persons with MCI have a more rapid rate of shrinkage of important memory regions of brain than controls. These brain scans are potential markers for the disease. The search is on for ways to identify persons at risk ever earlier, before any obvious decline in function. Identifying these persons is important for development of drugs to combat the disease, for persons at risk being able to plan for their future, and for scientists trying to understand the early changes in brain which result in AD.

Using the newly-developed criteria for diagnosing persons with MCI, the NIA-funded Alzheimer's Disease Cooperative Study (ADCS) group, early this year, launched the first NIH trial to try to prevent persons with MCI from going on to develop AD. The agents being tested are the antioxidant vitamin E, and Aricept, one of the FDA-approved drugs for AD. Vital to the success of this trial is rapidly enrolling over 700 persons with MCI at over 70 sites nationwide and Canada.

Pathology of AD may begin long before clinical signs appear

Persons with MCI, who are autopsied after they die of other causes, already show loss of specific brain cells in the most vulnerable part of the brain affected by AD. Their brains already contain a large number of plaques and tangles, the hallmarks of AD. Even persons who have no obvious mental decline sometimes have large numbers of plaques and tangles and many scientists consider that they may be in the very early preclinical stages of AD. It is possible that the first AD changes in brain occur many years prior to the development of clinical symptoms.

Other avenues of research suggest that even prenatal events might affect the brain's ability to withstand the effects of aging. Food supplement studies in animals suggest prenatal levels of choline help maintain brain function in old age. And diets high in antioxidants in later life help maintain brain function in elderly rats. The "brain reserve" hypothesis suggests that the greater the number of healthy brain cells and connections formed during early life, the more reserve there will be in later life against the effects of brain damage such as those seen in AD. Exercise and mental stimulation also build up brain connections and even generate new brain cells from stem cell precursors in rodents, stimulating better blood delivery and production of "growth factors" that help brain cells survive. Investigation of whether these "low tech" interventions might help delay late life cognitive decline or even development of AD is continuing. Other avenues of investigation include whether cardiovascular risk factors, such as high blood pressure in mid-life might increase the risk of developing AD. Recent studies show that small strokes may exacerbate the clinical symptoms of AD in persons who have the disease.

From epidemiology, clinical, and laboratory studies to clinical trials

A number of epidemiology and clinical studies have shown that persons who take anti-inflammatory drugs and postmenopausal women who take estrogen are at lower risk of developing AD than their peers; and recent results link low folate levels in blood to a higher risk of developing AD. The epidemiological studies are supported by laboratory studies. However, the only way to tell whether agents such as estrogen or anti-inflammatory drugs will prevent or slow AD progression is to test them in clinical trials. A number of such trials are now being funded. They test drugs either for their ability to slow the progression of AD or for their ability to slow age-related memory impairment and development of AD.

Slowing progression of AD

The Alzheimer's disease Cooperative Study (ADCS) is:

- Completing the first trial on a steroidal anti-inflammatory drug, prednisone.
- Completing a pilot trial on estrogen.
- Beginning a trial to test a non-steroidal anti-inflammatory drug and one fo the new Cox2 inhibitors.

Slowing progression of memory impairment and development of AD

New trials include:

- A trial to test the effect of estrogen in women at risk for AD.
- An add-on to the ongoing Women's Health Study to test the effects of the antioxidant, vitamin E, and the anti-inflammatory, aspirin.
- An add-on to the ongoing Women's Antioxidant Cardiovascular Study to test the effects of antioxidants (vitamins E, C, or beta carotene) or of a folate/vitamin B combination.
- A request for applications to test the dietary supplement Ginkgo biloba.

As the only way at present to test whether a drug is effective is to monitor the slow decline in brain function, these trials take several years. Adding to the time factor are delays in recruiting enough suitable persons to participate. Ways to improve recruitment strategies, as well as to more rapidly chart decline, are being sought.

Genetic and molecular research is beginning to identify targets for future therapies

The clinical trials described above could be started rapidly because the agents they are testing are already approved for human use. The next generation of drugs will be completely new ones developed to combat specific brain pathways that are involved in the disease. These drugs will need to go through the necessary regulatory steps: testing for efficacy in the test tube and for safety and efficacy in animals, then in humans, before being tested for efficacy in AD patients. Clues to how AD can start come from the exciting work identifying mutated genes (amyloid precursor protein, presenilins) responsible for inherited early onset AD genes and from identification of risk factor genes, such as ApoE4, for late onset disease. Unraveling the pathways leading from these gene changes to disease is providing a wealth of potential sites at which the progression of AD in the brain might be blocked. Transgenic mice carrying the mutated genes show much of the pathology of AD as they age. These mice are being used to study the progression of disease changes, the relationship between abnormal changes in the brain and loss of mental function, and to provide a model in which possible therapies can be directly tested.

Leads for promising avenues of research

Plaques and tangles are the pathophysiological hallmarks of AD. Our goals are to reduce synthesis of precursors, stop aggregation, solubilize deposits, and stop downstream effects. Related to cell death dysfunction, efforts are underway to increase levels of protective growth factors, interfere with cell death pathways and boost ailing cells. In the long term, our goal is to replace dying cells and boost levels of growth factors by employing genetic engineering strategies. Efforts are also focused on stopping the loss of connections between neurons that occurs in AD.

Behavioral and caregiver research

Research has also been focussed on behavioral and medication strategies to manage the most troubling of the behavioral and other consequences of AD - wandering, aggression, agitation, sleep problems, and incontinence. Interventions are being systematically developed and tested to ameliorate these symptoms. Some include the beneficial effects of exercise, sleep hygiene, and strategies for coping with activities of daily living on reducing agitation and other negative behaviors. Better control of these behaviors will improve care and delay institutionalization. Related research focuses on reducing the effects of caregiving on the health and well-being of the caregivers; the stress of caregiving may lead to reduced immune function and increased susceptibility to disease. As another part of this effort, family-relevant measures of patient function are being developed by the Caregiving, Health Services, and Outcomes

Research in Dementia (CHORD) project.

The increasing prevalence of AD crosses all ethnic groups. As part of the NIA Alzheimer's Disease Prevention Initiative, the NIA is supporting research aimed at developing caregiving interventions specifically tailored for minority families. Caregiving in minority populations is now being explored in the six sites of the REACH (Resources for Enhancing Alzheimer's Caregiver Health) initiative. This NIH study is designed to test social and behavioral interventions that would enhance family caregiving techniques in these populations.

None of these initiatives will be effective if persons with AD are not efficiently diagnosed and treated by their physician. Practice guidelines for diagnosis have been drawn up by the Agency for Health Care Policy and Research and practice guidelines for treatment by the American Psychiatric Association. Regular physician updates in research and care are carried out at the 28 NIA Alzheimer Disease Centers across the country.

The NIA is also taking steps to make information about AD more accessible to the general public. The NIA's Alzheimer's Disease Education and Referral (ADEAR) Center provides education services to the community through its web site (www.alzheimers.org) and a toll-free number (800-438-4380). In collaboration with the FDA, ADEAR had developed a database of ongoing AD clinical trials. When complete, both government and commercial trials will be represented. The database is accessible through the ADEAR site. Information can also be obtained through trained information specialists on the ADEAR toll-free line. Information on NIA-funded Ad trials is now available, and ADEAR is soliciting information about ongoing clinical trials being conducted by drug companies.

Conclusion

The AD Prevention Initiative addresses a major source of disability in older persons, and its success in delaying progression of symptoms will contribute substantially to the projected cost savings described in the Alliance report. The National Institute on Aging, as the lead Federal agency on AD research, is committed to continuing its support of basic, clinical, and behavioral research that will improve our understanding of this devastating disease and help prevent or delay the onset of its symptoms.